DOCKET NO: 1587-0024-0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
KAZUNORI SAITOH ET AL	: EXAMINER: CHIN, C. L.
SERIAL NO: 08/893,759	:
FILED: JULY 11, 1997	: GROUP ART UNIT: 1641

FOR: STEP AGGLUTINATION IMMUNOASSAY

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal from the Final Rejection of the claims dated July 2, 2003.

I. REAL PARTY IN INTEREST

The real party in interest is Daiichi Pure Chemicals Co., LTD. of Tokyo, Japan, by assignment recorded January 16, 2003 at Reel/Frame 013670/0233.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 7-42 are pending in this application. The appealed claims are Claims 7-16, 18-30, 32-35, and 39. Claims 17, 31, 36-38, and 40-42 have been withdrawn from consideration.

IV. STATUS OF THE AMENDMENTS FILED UNDER 37 C.F.R. §1.116

No amendment has been filed subsequent to the mailing of the Final Rejection on July 2, 2003.

V. THE APPEALED CLAIMS

A copy of the appealed claims is submitted in the Appendix attached hereto.

VI. SUMMARY OF THE INVENTION

The present invention relates to an agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is immobilized on an insoluble carrier, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is free,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

See the specification at page 4, line 19 to page 5, line 75; page 8, lines 7-25.

The present invention also relates to immunoassay described above, where said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the amount of the antigen in the sample is determined from a calibration curve. See the specification at page 9, line 11.

The present invention also relates to the immunoassay described above, where the sample contains an undetectable amount of the antigen. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the sample contains a detectable quantity of the antigen. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms. See the specification at page 6, line18 to page 7, line 4.

The present invention also relates to the immunoassay described above, where the insoluble carrier is a latex particle. See the specification at page 6, line 25.

The present invention also relates to the immunoassay described above, where the insoluble carrier is silica or alumina. See the specification at page 7, line 2.

The present invention also relates to the immunoassay described above, where the insoluble carrier has an average particle size of 0.05 to 1 μm. See the specification at page 7, line 6.

The present invention also relates to the immunoassay described above, where the sample is a buffered aqueous solution. See the specification at page 7, lines 12-14.

The present invention also relates to the immunoassay described above, where the sample does not contain an immune reaction-accelerating component. See the specification at page 10, lines 2-3.

The present invention also relates to the immunoassay described above, where the immune reaction-accelerating component is polyethylene glycol 6000. See the specification at page 10, line 1.

The present invention also relates to the immunoassay described above, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody. See the specification at page 7, line 21 to page 8, line 6.

The present invention also relates to an agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is free, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is immobilized on an insoluble carrier,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

See the specification at page 4, line 19 to page 5, line 19 and page 8, lines 7-25.

VII. THE ISSUES OF THIS APPEAL

(1) Whether Claims 7, 10-13, and 18-19 are unpatentable under 35 U.S.C. §103(a) over Strahilevitz (U.S. Patent No. 4,375,414) in view of Schmidtberger (U.S. Patent No. 4,375,414) or Young et al. (U.S. Patent No. 5,460,947).

(2) Whether Claims 21-27, 29, 30, and 32-34 are unpatentable under 35 U.S.C. §103(a) over Boehringer Mannheim GMBH (EP 617 285, hereinafter referred to as "EP '285") in view of Schmidtberger or Young et al.

(3) Whether Claims 21-27, 29, 30, and 32-34 are unpatentable under 35 U.S.C. §103(a) over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al.

VIII. GROUPING OF THE CLAIMS

The claims do not stand or fall together. The reason for them not standing or falling together with the other claims will be pointed out and discussed below.

IX. ARGUMENTS IN TRAVERSAL OF THE REJECTION

Using an immunoassay comprising the binding of two antibodies and an antigen, the optical measurement of the agglutinate became possible for the first time with the present invention, by means of the coexistence of the immobilized antibody not agglutinated by

itself, the free antibody, and the antibody. An important feature of the claimed methods is that two antibodies are used to bind the antigen, and each antibody is contacted with the sample sequentially to form an agglutinate comprising the antigen and the two antibodies (see (i) and (ii) in Claims 7 and 21. Another important feature is that the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin- antithrombin III complex.

The present inventors have discovered that the two-step antibody binding reaction of the present in provides an assay method having high specificity and low cost.

1. Claims 7, 10-13, and 18-19 are Not Obvious over Strahilevitz in view of Schmidtberger or Young et al.

Strahilevitz describes immunoassays of psychoactive drugs (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. Moreover, there is no suggestion or motivation from Strahilevitz to detect those antigens.

Strahilevitz's purpose is only to detect a relatively small molecular substance called "hapten," and its antigenic determinant is also limited. This method requires a cleansing step between the first reaction and the second reaction, and the state of the completed reaction is evaluated by visual observation, and not by optical observation (cf. difference of absorbance). In contrast, the present invention intends to detect proteins expected to have at least two antigenic determinants, and no cleaning step is required during the reaction process. The present invention also uses the optical measurement for the evaluation of the final state of reactions.

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2). This reference fails to describe the use of antibodies to assay for psychoactive drugs.

Schmidtberger's invention relates to an agglutination assay using antibodies specific for apoprotein B, and describes use of both the monoclonal antibody and the polyclonal antibody. Nevertheless, these are used as the antibodies immobilized on an insoluble carrier, and the description that these are used as free antibodies is nowhere found in this reference. Moreover, this method requires an interrupted step needed for cleansing between the first reaction and the second reaction, and the reaction solution resulted from the agglutinative reaction must be measured by the visual observation, not by the optical observation. Thus, there is obviously disadvantage in this method, compared with the present invention.

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5). This reference fails to describe the use of antibodies to assay for psychoactive drugs.

Young et al. relates to the ELISA method or the EIA method using antibodies specific for apoprotein B, and describes use of both the monoclonal antibody and the polyclonal antibody. However, these are antibodies which are immobilized on an insoluble carrier and then labeled with an enzyme, and the description that these are used as free antibodies is nowhere found in this reference. Moreover, this method is indispensably required to take a cleansing step between the first reaction and the second reaction in order to remove the non-reactive materials from the solution. Thus there is obviously disadvantage in this method, compared with the present invention.

The Examiner's rejection is based on the assertion that one of ordinary skill in the art would (1) modify the assay described in Strahilevitz so that apoprotein B was the assay target instead of the psychoactive drugs specified in that reference and (2) use the antibodies described in Schmidtberger or Young et al. in place of the antibodies described in Strahilevitz. See the Official Action dated June 16, 2002 at page 4, second paragraph.

However, the Examiner has not explained, in any fashion whatsoever, ***why*** one would be motivated to make these modifications. Without such an explanation, the rejection is unsustainable for this ground alone.

The fact of the matter is that Schmidtberger and Young et al. each describe a method of using antibodies to assay for apoprotein B. Strahilevitz, on the other hand, describes a method of assaying for psychoactive drugs, not apoprotein B. The Examiner has provided no explanation ***why*** one would be motivated to modify the psychoactive drug assay method described in Strahilevitz to target apoprotein B based on the teachings of Schmidtberger or Young et al. when the latter two references themselves relate to an assay for apoprotein B.

In view of the foregoing, Claims 7, 10-13, and 18-19 are not obvious over Strahilevitz in view of Schmidtberger or Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination references.

2. Claims 21-27, 29, 30, and 32-34 are Not Obvious over EP '285 in view of Schmidtberger or Young et al.

EP '285 describes a method for reducing the Hook effect in immunoassays with particulate carriers (see the Title and the Abstract). The reference describes a method for determining an analyte consisting of the antibody immobilized on a particular carrier and an antigen. However, this reference is quite silent on any use of the free antibody which is essential for the agglutination of the present invention. Especially, attention should be directed to the description on page 4, lines 16-19 of this reference, which reads as follows:

> It should be pointed out at this point that in the preferred form of embodiment of the present invention shown in Figure 2, the soluble receptor R2 is chosen so that the binding of R2 to the analyte does not interfere with the binding of immobilized receptor R1 to the analyte, i.e., the soluble receptor R2 recognizes a different epitope on the analyte than the immobilized receptors Ra, R1b, and the binding of R2 to the analyte has no significant effect on the binding of R1a and R1b to the analyte.

Thus, this method must be carried out under such specific conditions, to avoid the phenomenon where the binding of R1 would otherwise be affected by the binding of the immobilized R1 to the analyte. As a consequence, this method is too expensive and time wasting to be industrially adopted. In contrast, the present invention is free from such restrictions.

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2).

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5).

The Examiner has failed to provide any evidence to demonstrate that one skilled in the art would have a reasonable expectation that the antibodies described in Schmidtberger or Young et al. would actually work in the assay described by EP '285 and reduce the Hook effect. In the absence of this evidence, the rejection is unsustainable and must be withdrawn.

In view of the foregoing, Claims 21-27, 29, 30, and 32-34 are not obvious over EP '285 in view of Schmidtberger or Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination of references.

3. Claims 21-27, 29, 30, and 32-34 are Not Obvious over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al.

Cragle et al. describe an immunoassay method (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. The Examiner argues that Cragle et al. discloses an improved nephelometric immunoassay for an antigen in a fluid sample comprising contacting the sample with both a solid phase antibody and liquid phase

antibody and measuring the amount of formed complexes, i.e., agglutinates, wherein the Hook effect is avoided (see page 4 of the Office Action dated July 16, 2002). However, use of the immobilized antibody is described only in the context with the sandwich immunoassay (note: this assay is not usable for the detection of agglutinate), but not in the context with nephelometric immunoassay even though use of the free antibody is described in this context. In this reference's sandwich immunoassay using the solid phase antibody and liquid phase antibody, it is imperative that the liquid phase antibodies be labeled and non-reactive residues be removed. In contrast, the present invention is free from both of the labeling of free antibodies and the removing of non-reactive residues of immobilized antibodies and free antibodies.

Strahilevitz describes immunoassays of psychoactive drugs (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. Moreover, there is no suggestion or motivation from Strahilevitz to detect those antigens.

EP '285 describes a method for reducing the Hook effect in immunoassays with particulate carriers (see the Title and the Abstract).

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2).

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5).

The Examiner acknowledges that Cragle et al. fails to describe, *inter alia*, (1) sequential contact of two antibodies and (2) the use of antibodies specific for apoprotein B.

The Examiner asserts that it would obvious to one of ordinary skill to modify the method described in Cragle et al. to include (1) in view of the teachings of Strahilevitz or EP

'285 and to include (2) based on the teachings of Schmidtberger or Young et al. See the Official Action dated July 16, 2002 from the last full paragraph at page 6 to the end of the paragraph bridging page 7.

However, the Examiner has provided no evidence as to ***why*** one would be motivated to make either of these modifications to the assay describe in Cragle et al. The Examiner has simply stated that the modifications would "be obvious to one of ordinary skill in the art." Without such evidence, no motivation has been established which would render the claimed immunoassay obvious in view of the cited references.

In view of the foregoing, Claims 21-27, 29, 30, and 32-34 are not obvious over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination of references.

4. Claims 8 and 22

Claims 8 and 22 specify that the optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 8 and 22 are unpatentable under 35 U.S.C. §103(a).

5. Claims 9 and 23

Claims 9 and 23 specify that the amount of the antigen in the sample is determined from a calibration curve. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2,

2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 9 and 23 are unpatentable under 35 U.S.C. §103(a).

6. Claims 10 and 24

Claims 10 and 24 specify the sample contains an undetectable amount of the antigen. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 10 and 24 are unpatentable under 35 U.S.C. §103(a).

7. Claims 11 and 25

Claims 11 and 25 specify the sample contains a detectable quantity of the antigen. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 11 and 25 are unpatentable under 35 U.S.C. §103(a).

8. Claims 12 and 26

Claims 12 and 26 specify that the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 12 and 26 are unpatentable under 35 U.S.C. §103(a).

9. Claims 13 and 27

Claims 13 and 27 specify that the insoluble carrier is a latex particle. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 13 and 27 are unpatentable under 35 U.S.C. §103(a).

10. Claims 14 and 28

Claims 14 and 28 specify that the insoluble carrier is silica or alumina. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 14 and 28 are unpatentable under 35 U.S.C. §103(a).

11. Claims 15 and 29

Claims 15 and 29 specify the insoluble carrier has an average particle size of 0.05 to 1 μm. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 15 and 29 are unpatentable under 35 U.S.C. §103(a).

12. Claims 16 and 30

Claims 16 and 30 specify that the sample is a buffered aqueous solution. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002.

Therefore, the Examiner has failed to meet the burden of proof that that Claims 16 and 30 are unpatentable under 35 U.S.C. §103(a).

13. Claims 18 and 32

Claims 18 and 32 specify the sample does not contain an immune reaction-accelerating component. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 18 and 32 are unpatentable under 35 U.S.C. §103(a).

14. Claims 19 and 33

Claims 19 and 33 specify that the immune reaction-accelerating component is polyethylene glycol 6000. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 19 and 33 are unpatentable under 35 U.S.C. §103(a).

15. Claims 20 and 34

Claims 20 and 34 specify that the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 20 and 34 are unpatentable under 35 U.S.C. §103(a).

16. Claims 35 and 39

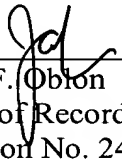
Claims 35 and 39 specify that the antigen is apoprotein B. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 35 and 39 are unpatentable under 35 U.S.C. §103(a).

X. RELIEF REQUESTED

Reversal of the Examiner's rejections of the appealed claims under 35 U.S.C. § 103(a) is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

James J. Kelly, PhD
Registration No. 41,504

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/03)

APPENDIX

The appealed claims, i.e., Claims 7-16, 18-30, 32-35, and 39 read as follows:

7. An agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is immobilized on an insoluble carrier, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is free,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

8. The immunoassay of Claim 7, wherein said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate.

9. The immunoassay according to Claim 7, wherein the amount of the antigen in the sample is determined from a calibration curve.

10. The immunoassay of Claim 7, wherein the sample contains an undetectable amount of the antigen.

11. The immunoassay of Claim 7, wherein the sample contains a detectable quantity of the antigen.

12. The immunoassay of Claim 7, wherein the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms.

13. The immunoassay according to Claim 7, wherein the insoluble carrier is a latex particle.

14. The immunoassay of Claim 7, wherein the insoluble carrier is silica or alumina.

15. The immunoassay of Claim 7, wherein the insoluble carrier has an average particle size of 0.05 to 1 μm.

16. The immunoassay of Claim 7, wherein the sample is a buffered aqueous solution.

18. The immunoassay of Claim 7, wherein the sample does not contain an immune reaction-accelerating component.

19. The immunoassay of Claim 18, wherein the immune reaction-accelerating component is polyethylene glycol 6000.

20. The immunoassay of Claim 18, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody.

21. An agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is free, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is immobilized on an insoluble carrier,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

22. The immunoassay of Claim 21, wherein said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate.

23. The immunoassay according to Claim 21, wherein the amount of the antigen in the sample is determined from a calibration curve.

24. The immunoassay of Claim 21, wherein the sample contains an undetectable amount of the antigen.

25. The immunoassay of Claim 21, wherein the sample contains a detectable quantity of the antigen.

26. The immunoassay of Claim 21, wherein the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms.

27. The immunoassay according to Claim 21, wherein the insoluble carrier is a latex particle.

28. The immunoassay of Claim 21, wherein the insoluble carrier is silica or alumina.

29. The immunoassay of Claim 21, wherein the insoluble carrier has an average particle size of 0.05 to 1 μm.

30. The immunoassay of Claim 21, wherein the sample is a buffered aqueous solution.

32. The immunoassay of Claim 21, wherein the sample does not contain an immune reaction-accelerating component.

33. The immunoassay of Claim 32, wherein the immune reaction-accelerating component is polyethylene glycol 6000.

34. The immnuoassay of Claim 21, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody.

35. The immunoassay of Claim 7, wherein the antigen is apoprotein B.

39. The immunoassay of Claim 21, wherein the antigen is apoprotein B.

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KAZUNORI SAITOH ET AL	: EXAMINER: CHIN, C. L.
SERIAL NO: 08/893,759	:
FILED: JULY 11, 1997	: GROUP ART UNIT: 1641

FOR: STEP AGGLUTINATION IMMUNOASSAY

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal from the Final Rejection of the claims dated July 2, 2003.

I. REAL PARTY IN INTEREST

The real party in interest is Daiichi Pure Chemicals Co., LTD. of Tokyo, Japan, by assignment recorded January 16, 2003 at Reel/Frame 013670/0233.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 7-42 are pending in this application. The appealed claims are Claims 7-16, 18-30, 32-35, and 39. Claims 17, 31, 36-38, and 40-42 have been withdrawn from consideration.

IV. STATUS OF THE AMENDMENTS FILED UNDER 37 C.F.R. §1.116

No amendment has been filed subsequent to the mailing of the Final Rejection on July 2, 2003.

V. THE APPEALED CLAIMS

A copy of the appealed claims is submitted in the Appendix attached hereto.

VI. SUMMARY OF THE INVENTION

The present invention relates to an agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is immobilized on an insoluble carrier, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is free,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

See the specification at page 4, line 19 to page 5, line 75; page 8, lines 7-25.

The present invention also relates to immunoassay described above, where said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the amount of the antigen in the sample is determined from a calibration curve. See the specification at page 9, line 11.

The present invention also relates to the immunoassay described above, where the sample contains an undetectable amount of the antigen. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the sample contains a detectable quantity of the antigen. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms. See the specification at page 6, line18 to page 7, line 4.

The present invention also relates to the immunoassay described above, where the insoluble carrier is a latex particle. See the specification at page 6, line 25.

The present invention also relates to the immunoassay described above, where the insoluble carrier is silica or alumina. See the specification at page 7, line 2.

The present invention also relates to the immunoassay described above, where the insoluble carrier has an average particle size of 0.05 to 1 μm. See the specification at page 7, line 6.

The present invention also relates to the immunoassay described above, where the sample is a buffered aqueous solution. See the specification at page 7, lines 12-14.

The present invention also relates to the immunoassay described above, where the sample does not contain an immune reaction-accelerating component. See the specification at page 10, lines 2-3.

The present invention also relates to the immunoassay described above, where the immune reaction-accelerating component is polyethylene glycol 6000. See the specification at page 10, line 1.

The present invention also relates to the immunoassay described above, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody. See the specification at page 7, line 21 to page 8, line 6.

The present invention also relates to an agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is free, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is immobilized on an insoluble carrier,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

See the specification at page 4, line 19 to page 5, line 19 and page 8, lines 7-25.

VII. THE ISSUES OF THIS APPEAL

(1) Whether Claims 7, 10-13, and 18-19 are unpatentable under 35 U.S.C. §103(a) over Strahilevitz (U.S. Patent No. 4,375,414) in view of Schmidtberger (U.S. Patent No. 4,375,414) or Young et al. (U.S. Patent No. 5,460,947).

(2) Whether Claims 21-27, 29, 30, and 32-34 are unpatentable under 35 U.S.C. §103(a) over Boehringer Mannheim GMBH (EP 617 285, hereinafter referred to as "EP '285") in view of Schmidtberger or Young et al.

(3) Whether Claims 21-27, 29, 30, and 32-34 are unpatentable under 35 U.S.C. §103(a) over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al.

VIII. GROUPING OF THE CLAIMS

The claims do not stand or fall together. The reason for them not standing or falling together with the other claims will be pointed out and discussed below.

IX. ARGUMENTS IN TRAVERSAL OF THE REJECTION

Using an immunoassay comprising the binding of two antibodies and an antigen, the optical measurement of the agglutinate became possible for the first time with the present invention, by means of the coexistence of the immobilized antibody not agglutinated by

itself, the free antibody, and the antibody. An important feature of the claimed methods is that two antibodies are used to bind the antigen, and each antibody is contacted with the sample sequentially to form an agglutinate comprising the antigen and the two antibodies (see (i) and (ii) in Claims 7 and 21. Another important feature is that the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin- antithrombin III complex.

The present inventors have discovered that the two-step antibody binding reaction of the present in provides an assay method having high specificity and low cost.

1. Claims 7, 10-13, and 18-19 are Not Obvious over Strahilevitz in view of Schmidtberger or Young et al.

Strahilevitz describes immunoassays of psychoactive drugs (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. Moreover, there is no suggestion or motivation from Strahilevitz to detect those antigens.

Strahilevitz's purpose is only to detect a relatively small molecular substance called "hapten," and its antigenic determinant is also limited. This method requires a cleansing step between the first reaction and the second reaction, and the state of the completed reaction is evaluated by visual observation, and not by optical observation (cf. difference of absorbance). In contrast, the present invention intends to detect proteins expected to have at least two antigenic determinants, and no cleaning step is required during the reaction process. The present invention also uses the optical measurement for the evaluation of the final state of reactions.

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2). This reference fails to describe the use of antibodies to assay for psychoactive drugs.

Schmidtberger's invention relates to an agglutination assay using antibodies specific for apoprotein B, and describes use of both the monoclonal antibody and the polyclonal antibody. Nevertheless, these are used as the antibodies immobilized on an insoluble carrier, and the description that these are used as free antibodies is nowhere found in this reference. Moreover, this method requires an interrupted step needed for cleansing between the first reaction and the second reaction, and the reaction solution resulted from the agglutinative reaction must be measured by the visual observation, not by the optical observation. Thus, there is obviously disadvantage in this method, compared with the present invention.

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5). This reference fails to describe the use of antibodies to assay for psychoactive drugs.

Young et al. relates to the ELISA method or the EIA method using antibodies specific for apoprotein B, and describes use of both the monoclonal antibody and the polyclonal antibody. However, these are antibodies which are immobilized on an insoluble carrier and then labeled with an enzyme, and the description that these are used as free antibodies is nowhere found in this reference. Moreover, this method is indispensably required to take a cleansing step between the first reaction and the second reaction in order to remove the non-reactive materials from the solution. Thus there is obviously disadvantage in this method, compared with the present invention.

The Examiner's rejection is based on the assertion that one of ordinary skill in the art would (1) modify the assay described in Strahilevitz so that apoprotein B was the assay target instead of the psychoactive drugs specified in that reference and (2) use the antibodies described in Schmidtberger or Young et al. in place of the antibodies described in Strahilevitz. See the Official Action dated June 16, 2002 at page 4, second paragraph.

However, the Examiner has not explained, in any fashion whatsoever, ***why*** one would be motivated to make these modifications. Without such an explanation, the rejection is unsustainable for this ground alone.

The fact of the matter is that Schmidtberger and Young et al. each describe a method of using antibodies to assay for apoprotein B. Strahilevitz, on the other hand, describes a method of assaying for psychoactive drugs, not apoprotein B. The Examiner has provided no explanation ***why*** one would be motivated to modify the psychoactive drug assay method described in Strahilevitz to target apoprotein B based on the teachings of Schmidtberger or Young et al. when the latter two references themselves relate to an assay for apoprotein B.

In view of the foregoing, Claims 7, 10-13, and 18-19 are not obvious over Strahilevitz in view of Schmidtberger or Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination references.

2. Claims 21-27, 29, 30, and 32-34 are Not Obvious over EP '285 in view of Schmidtberger or Young et al.

EP '285 describes a method for reducing the Hook effect in immunoassays with particulate carriers (see the Title and the Abstract). The reference describes a method for determining an analyte consisting of the antibody immobilized on a particular carrier and an antigen. However, this reference is quite silent on any use of the free antibody which is essential for the agglutination of the present invention. Especially, attention should be directed to the description on page 4, lines 16-19 of this reference, which reads as follows:

> It should be pointed out at this point that in the preferred form of embodiment of the present invention shown in Figure 2, the soluble receptor R2 is chosen so that the binding of R2 to the analyte does not interfere with the binding of immobilized receptor R1 to the analyte, i.e., the soluble receptor R2 recognizes a different epitope on the analyte than the immobilized receptors Ra, R1b, and the binding of R2 to the analyte has no significant effect on the binding of R1a and R1b to the analyte.

Thus, this method must be carried out under such specific conditions, to avoid the phenomenon where the binding of R1 would otherwise be affected by the binding of the immobilized R1 to the analyte. As a consequence, this method is too expensive and time wasting to be industrially adopted. In contrast, the present invention is free from such restrictions.

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2).

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5).

The Examiner has failed to provide any evidence to demonstrate that one skilled in the art would have a reasonable expectation that the antibodies described in Schmidtberger or Young et al. would actually work in the assay described by EP '285 and reduce the Hook effect. In the absence of this evidence, the rejection is unsustainable and must be withdrawn.

In view of the foregoing, Claims 21-27, 29, 30, and 32-34 are not obvious over EP '285 in view of Schmidtberger or Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination of references.

3. Claims 21-27, 29, 30, and 32-34 are Not Obvious over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al.

Cragle et al. describe an immunoassay method (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. The Examiner argues that Cragle et al. discloses an improved nephelometric immunoassay for an antigen in a fluid sample comprising contacting the sample with both a solid phase antibody and liquid phase

antibody and measuring the amount of formed complexes, i.e., agglutinates, wherein the Hook effect is avoided (see page 4 of the Office Action dated July 16, 2002). However, use of the immobilized antibody is described only in the context with the sandwich immunoassay (note: this assay is not usable for the detection of agglutinate), but not in the context with nephelometric immunoassay even though use of the free antibody is described in this context. In this reference's sandwich immunoassay using the solid phase antibody and liquid phase antibody, it is imperative that the liquid phase antibodies be labeled and non-reactive residues be removed. In contrast, the present invention is free from both of the labeling of free antibodies and the removing of non-reactive residues of immobilized antibodies and free antibodies.

Strahilevitz describes immunoassays of psychoactive drugs (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. Moreover, there is no suggestion or motivation from Strahilevitz to detect those antigens.

EP '285 describes a method for reducing the Hook effect in immunoassays with particulate carriers (see the Title and the Abstract).

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2).

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5).

The Examiner acknowledges that Cragle et al. fails to describe, *inter alia*, (1) sequential contact of two antibodies and (2) the use of antibodies specific for apoprotein B.

The Examiner asserts that it would obvious to one of ordinary skill to modify the method described in Cragle et al. to include (1) in view of the teachings of Strahilevitz or EP

'285 and to include (2) based on the teachings of Schmidtberger or Young et al. See the Official Action dated July 16, 2002 from the last full paragraph at page 6 to the end of the paragraph bridging page 7.

However, the Examiner has provided no evidence as to ***why*** one would be motivated to make either of these modifications to the assay describe in Cragle et al. The Examiner has simply stated that the modifications would "be obvious to one of ordinary skill in the art." Without such evidence, no motivation has been established which would render the claimed immunoassay obvious in view of the cited references.

In view of the foregoing, Claims 21-27, 29, 30, and 32-34 are not obvious over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination of references.

4. Claims 8 and 22

Claims 8 and 22 specify that the optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 8 and 22 are unpatentable under 35 U.S.C. §103(a).

5. Claims 9 and 23

Claims 9 and 23 specify that the amount of the antigen in the sample is determined from a calibration curve. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2,

2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 9 and 23 are unpatentable under 35 U.S.C. §103(a).

6. Claims 10 and 24

Claims 10 and 24 specify the sample contains an undetectable amount of the antigen. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 10 and 24 are unpatentable under 35 U.S.C. §103(a).

7. Claims 11 and 25

Claims 11 and 25 specify the sample contains a detectable quantity of the antigen. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 11 and 25 are unpatentable under 35 U.S.C. §103(a).

8. Claims 12 and 26

Claims 12 and 26 specify that the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 12 and 26 are unpatentable under 35 U.S.C. §103(a).

9. Claims 13 and 27

Claims 13 and 27 specify that the insoluble carrier is a latex particle. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 13 and 27 are unpatentable under 35 U.S.C. §103(a).

10. Claims 14 and 28

Claims 14 and 28 specify that the insoluble carrier is silica or alumina. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 14 and 28 are unpatentable under 35 U.S.C. §103(a).

11. Claims 15 and 29

Claims 15 and 29 specify the insoluble carrier has an average particle size of 0.05 to 1 μm. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 15 and 29 are unpatentable under 35 U.S.C. §103(a).

12. Claims 16 and 30

Claims 16 and 30 specify that the sample is a buffered aqueous solution. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002.

Therefore, the Examiner has failed to meet the burden of proof that that Claims 16 and 30 are unpatentable under 35 U.S.C. §103(a).

13. Claims 18 and 32

Claims 18 and 32 specify the sample does not contain an immune reaction-accelerating component. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 18 and 32 are unpatentable under 35 U.S.C. §103(a).

14. Claims 19 and 33

Claims 19 and 33 specify that the immune reaction-accelerating component is polyethylene glycol 6000. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 19 and 33 are unpatentable under 35 U.S.C. §103(a).

15. Claims 20 and 34

Claims 20 and 34 specify that the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 20 and 34 are unpatentable under 35 U.S.C. §103(a).

16. Claims 35 and 39

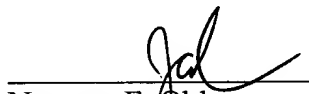
Claims 35 and 39 specify that the antigen is apoprotein B. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 35 and 39 are unpatentable under 35 U.S.C. §103(a).

X. RELIEF REQUESTED

Reversal of the Examiner's rejections of the appealed claims under 35 U.S.C. § 103(a) is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

James J. Kelly, PhD
Registration No. 41,504

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/03)

APPENDIX

The appealed claims, i.e., Claims 7-16, 18-30, 32-35, and 39 read as follows:

7. An agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is immobilized on an insoluble carrier, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is free,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

8. The immunoassay of Claim 7, wherein said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate.

9. The immunoassay according to Claim 7, wherein the amount of the antigen in the sample is determined from a calibration curve.

10. The immunoassay of Claim 7, wherein the sample contains an undetectable amount of the antigen.

11. The immunoassay of Claim 7, wherein the sample contains a detectable quantity of the antigen.

12. The immunoassay of Claim 7, wherein the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms.

13. The immunoassay according to Claim 7, wherein the insoluble carrier is a latex particle.

14. The immunoassay of Claim 7, wherein the insoluble carrier is silica or alumina.

15. The immunoassay of Claim 7, wherein the insoluble carrier has an average particle size of 0.05 to 1 μm.

16. The immunoassay of Claim 7, wherein the sample is a buffered aqueous solution.

18. The immunoassay of Claim 7, wherein the sample does not contain an immune reaction-accelerating component.

19. The immunoassay of Claim 18, wherein the immune reaction-accelerating component is polyethylene glycol 6000.

20. The immunoassay of Claim 18, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody.

21. An agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is free, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is immobilized on an insoluble carrier,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

22. The immunoassay of Claim 21, wherein said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate.

23. The immunoassay according to Claim 21, wherein the amount of the antigen in the sample is determined from a calibration curve.

24. The immunoassay of Claim 21, wherein the sample contains an undetectable amount of the antigen.

25. The immunoassay of Claim 21, wherein the sample contains a detectable quantity of the antigen.

26. The immunoassay of Claim 21, wherein the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms.

27. The immunoassay according to Claim 21, wherein the insoluble carrier is a latex particle.

28. The immunoassay of Claim 21, wherein the insoluble carrier is silica or alumina.

29. The immunoassay of Claim 21, wherein the insoluble carrier has an average particle size of 0.05 to 1 μm.

30. The immunoassay of Claim 21, wherein the sample is a buffered aqueous solution.

32. The immunoassay of Claim 21, wherein the sample does not contain an immune reaction-accelerating component.

33. The immunoassay of Claim 32, wherein the immune reaction-accelerating component is polyethylene glycol 6000.

34. The immnuoassay of Claim 21, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody.

35. The immunoassay of Claim 7, wherein the antigen is apoprotein B.

39. The immunoassay of Claim 21, wherein the antigen is apoprotein B.

DOCKET NO: 1587-0024-0

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
KAZUNORI SAITOH ET AL	: EXAMINER: CHIN, C. L.
SERIAL NO: 08/893,759	:
FILED: JULY 11, 1997	: GROUP ART UNIT: 1641

FOR: STEP AGGLUTINATION IMMUNOASSAY

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal from the Final Rejection of the claims dated July 2, 2003.

I. REAL PARTY IN INTEREST

The real party in interest is Daiichi Pure Chemicals Co., LTD. of Tokyo, Japan, by assignment recorded January 16, 2003 at Reel/Frame 013670/0233.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 7-42 are pending in this application. The appealed claims are Claims 7-16, 18-30, 32-35, and 39. Claims 17, 31, 36-38, and 40-42 have been withdrawn from consideration.

IV. STATUS OF THE AMENDMENTS FILED UNDER 37 C.F.R. §1.116

No amendment has been filed subsequent to the mailing of the Final Rejection on July 2, 2003.

V. THE APPEALED CLAIMS

A copy of the appealed claims is submitted in the Appendix attached hereto.

VI. SUMMARY OF THE INVENTION

The present invention relates to an agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is immobilized on an insoluble carrier, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is free,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

See the specification at page 4, line 19 to page 5, line 75; page 8, lines 7-25.

The present invention also relates to immunoassay described above, where said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the amount of the antigen in the sample is determined from a calibration curve. See the specification at page 9, line 11.

The present invention also relates to the immunoassay described above, where the sample contains an undetectable amount of the antigen. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the sample contains a detectable quantity of the antigen. See the specification at page 8, line 26 to page 9, line 11.

The present invention also relates to the immunoassay described above, where the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms. See the specification at page 6, line18 to page 7, line 4.

The present invention also relates to the immunoassay described above, where the insoluble carrier is a latex particle. See the specification at page 6, line 25.

The present invention also relates to the immunoassay described above, where the insoluble carrier is silica or alumina. See the specification at page 7, line 2.

The present invention also relates to the immunoassay described above, where the insoluble carrier has an average particle size of 0.05 to 1 μm. See the specification at page 7, line 6.

The present invention also relates to the immunoassay described above, where the sample is a buffered aqueous solution. See the specification at page 7, lines 12-14.

The present invention also relates to the immunoassay described above, where the sample does not contain an immune reaction-accelerating component. See the specification at page 10, lines 2-3.

The present invention also relates to the immunoassay described above, where the immune reaction-accelerating component is polyethylene glycol 6000. See the specification at page 10, line 1.

The present invention also relates to the immunoassay described above, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody. See the specification at page 7, line 21 to page 8, line 6.

The present invention also relates to an agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is free, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is immobilized on an insoluble carrier,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

See the specification at page 4, line 19 to page 5, line 19 and page 8, lines 7-25.

VII. THE ISSUES OF THIS APPEAL

(1) Whether Claims 7, 10-13, and 18-19 are unpatentable under 35 U.S.C. §103(a) over Strahilevitz (U.S. Patent No. 4,375,414) in view of Schmidtberger (U.S. Patent No. 4,375,414) or Young et al. (U.S. Patent No. 5,460,947).

(2) Whether Claims 21-27, 29, 30, and 32-34 are unpatentable under 35 U.S.C. §103(a) over Boehringer Mannheim GMBH (EP 617 285, hereinafter referred to as "EP '285") in view of Schmidtberger or Young et al.

(3) Whether Claims 21-27, 29, 30, and 32-34 are unpatentable under 35 U.S.C. §103(a) over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al.

VIII. GROUPING OF THE CLAIMS

The claims do not stand or fall together. The reason for them not standing or falling together with the other claims will be pointed out and discussed below.

IX. ARGUMENTS IN TRAVERSAL OF THE REJECTION

Using an immunoassay comprising the binding of two antibodies and an antigen, the optical measurement of the agglutinate became possible for the first time with the present invention, by means of the coexistence of the immobilized antibody not agglutinated by

itself, the free antibody, and the antibody. An important feature of the claimed methods is that two antibodies are used to bind the antigen, and each antibody is contacted with the sample sequentially to form an agglutinate comprising the antigen and the two antibodies (see (i) and (ii) in Claims 7 and 21. Another important feature is that the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin- antithrombin III complex.

The present inventors have discovered that the two-step antibody binding reaction of the present in provides an assay method having high specificity and low cost.

1. Claims 7, 10-13, and 18-19 are Not Obvious over Strahilevitz in view of Schmidtberger or Young et al.

Strahilevitz describes immunoassays of psychoactive drugs (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. Moreover, there is no suggestion or motivation from Strahilevitz to detect those antigens.

Strahilevitz's purpose is only to detect a relatively small molecular substance called "hapten," and its antigenic determinant is also limited. This method requires a cleansing step between the first reaction and the second reaction, and the state of the completed reaction is evaluated by visual observation, and not by optical observation (cf. difference of absorbance). In contrast, the present invention intends to detect proteins expected to have at least two antigenic determinants, and no cleaning step is required during the reaction process. The present invention also uses the optical measurement for the evaluation of the final state of reactions.

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2). This reference fails to describe the use of antibodies to assay for psychoactive drugs.

Schmidtberger's invention relates to an agglutination assay using antibodies specific for apoprotein B, and describes use of both the monoclonal antibody and the polyclonal antibody. Nevertheless, these are used as the antibodies immobilized on an insoluble carrier, and the description that these are used as free antibodies is nowhere found in this reference. Moreover, this method requires an interrupted step needed for cleansing between the first reaction and the second reaction, and the reaction solution resulted from the agglutinative reaction must be measured by the visual observation, not by the optical observation. Thus, there is obviously disadvantage in this method, compared with the present invention.

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5). This reference fails to describe the use of antibodies to assay for psychoactive drugs.

Young et al. relates to the ELISA method or the EIA method using antibodies specific for apoprotein B, and describes use of both the monoclonal antibody and the polyclonal antibody. However, these are antibodies which are immobilized on an insoluble carrier and then labeled with an enzyme, and the description that these are used as free antibodies is nowhere found in this reference. Moreover, this method is indispensably required to take a cleansing step between the first reaction and the second reaction in order to remove the non-reactive materials from the solution. Thus there is obviously disadvantage in this method, compared with the present invention.

The Examiner's rejection is based on the assertion that one of ordinary skill in the art would (1) modify the assay described in Strahilevitz so that apoprotein B was the assay target instead of the psychoactive drugs specified in that reference and (2) use the antibodies described in Schmidtberger or Young et al. in place of the antibodies described in Strahilevitz. See the Official Action dated June 16, 2002 at page 4, second paragraph.

However, the Examiner has not explained, in any fashion whatsoever, ***why*** one would be motivated to make these modifications. Without such an explanation, the rejection is unsustainable for this ground alone.

The fact of the matter is that Schmidtberger and Young et al. each describe a method of using antibodies to assay for apoprotein B. Strahilevitz, on the other hand, describes a method of assaying for psychoactive drugs, not apoprotein B. The Examiner has provided no explanation ***why*** one would be motivated to modify the psychoactive drug assay method described in Strahilevitz to target apoprotein B based on the teachings of Schmidtberger or Young et al. when the latter two references themselves relate to an assay for apoprotein B.

In view of the foregoing, Claims 7, 10-13, and 18-19 are not obvious over Strahilevitz in view of Schmidtberger or Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination references.

2. Claims 21-27, 29, 30, and 32-34 are Not Obvious over EP '285 in view of Schmidtberger or Young et al.

EP '285 describes a method for reducing the Hook effect in immunoassays with particulate carriers (see the Title and the Abstract). The reference describes a method for determining an analyte consisting of the antibody immobilized on a particular carrier and an antigen. However, this reference is quite silent on any use of the free antibody which is essential for the agglutination of the present invention. Especially, attention should be directed to the description on page 4, lines 16-19 of this reference, which reads as follows:

> It should be pointed out at this point that in the preferred form of embodiment of the present invention shown in Figure 2, the soluble receptor R2 is chosen so that the binding of R2 to the analyte does not interfere with the binding of immobilized receptor R1 to the analyte, i.e., the soluble receptor R2 recognizes a different epitope on the analyte than the immobilized receptors Ra, R1b, and the binding of R2 to the analyte has no significant effect on the binding of R1a and R1b to the analyte.

Thus, this method must be carried out under such specific conditions, to avoid the phenomenon where the binding of R1 would otherwise be affected by the binding of the immobilized R1 to the analyte. As a consequence, this method is too expensive and time wasting to be industrially adopted. In contrast, the present invention is free from such restrictions.

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2).

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5).

The Examiner has failed to provide any evidence to demonstrate that one skilled in the art would have a reasonable expectation that the antibodies described in Schmidtberger or Young et al. would actually work in the assay described by EP '285 and reduce the Hook effect. In the absence of this evidence, the rejection is unsustainable and must be withdrawn.

In view of the foregoing, Claims 21-27, 29, 30, and 32-34 are not obvious over EP '285 in view of Schmidtberger or Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination of references.

3. Claims 21-27, 29, 30, and 32-34 are Not Obvious over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al.

Cragle et al. describe an immunoassay method (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. The Examiner argues that Cragle et al. discloses an improved nephelometric immunoassay for an antigen in a fluid sample comprising contacting the sample with both a solid phase antibody and liquid phase

antibody and measuring the amount of formed complexes, i.e., agglutinates, wherein the Hook effect is avoided (see page 4 of the Office Action dated July 16, 2002). However, use of the immobilized antibody is described only in the context with the sandwich immunoassay (note: this assay is not usable for the detection of agglutinate), but not in the context with nephelometric immunoassay even though use of the free antibody is described in this context. In this reference's sandwich immunoassay using the solid phase antibody and liquid phase antibody, it is imperative that the liquid phase antibodies be labeled and non-reactive residues be removed. In contrast, the present invention is free from both of the labeling of free antibodies and the removing of non-reactive residues of immobilized antibodies and free antibodies.

Strahilevitz describes immunoassays of psychoactive drugs (see the Abstract). The reference fails to describe apoprotein B, HbA_1C, serum amyloid A protein, or thrombin-antithrombin III complex as the antigen to be detected by the assay described therein. Moreover, there is no suggestion or motivation from Strahilevitz to detect those antigens.

EP '285 describes a method for reducing the Hook effect in immunoassays with particulate carriers (see the Title and the Abstract).

Schmidtberger describes an aggultination assay using antibodies which are specific for apoprotein B (see the Abstract and columns 1-2).

Young et al. describe two hybridomas which produce antibodies which immunoreact with apoprotein B and can be used as a diagnostic for the same (see the Abstract and columns 3-5).

The Examiner acknowledges that Cragle et al. fails to describe, *inter alia*, (1) sequential contact of two antibodies and (2) the use of antibodies specific for apoprotein B.

The Examiner asserts that it would obvious to one of ordinary skill to modify the method described in Cragle et al. to include (1) in view of the teachings of Strahilevitz or EP

'285 and to include (2) based on the teachings of Schmidtberger or Young et al. See the Official Action dated July 16, 2002 from the last full paragraph at page 6 to the end of the paragraph bridging page 7.

However, the Examiner has provided no evidence as to ***why*** one would be motivated to make either of these modifications to the assay describe in Cragle et al. The Examiner has simply stated that the modifications would "be obvious to one of ordinary skill in the art." Without such evidence, no motivation has been established which would render the claimed immunoassay obvious in view of the cited references.

In view of the foregoing, Claims 21-27, 29, 30, and 32-34 are not obvious over Cragle et al. in view of Strahilevitz, EP '285, Schmidtberger, and Young et al. Therefore, those claims are not unpatentable under 35 U.S.C. §103(a) over that combination of references.

4. Claims 8 and 22

Claims 8 and 22 specify that the optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 8 and 22 are unpatentable under 35 U.S.C. §103(a).

5. Claims 9 and 23

Claims 9 and 23 specify that the amount of the antigen in the sample is determined from a calibration curve. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2,

2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 9 and 23 are unpatentable under 35 U.S.C. §103(a).

6. Claims 10 and 24

Claims 10 and 24 specify the sample contains an undetectable amount of the antigen. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 10 and 24 are unpatentable under 35 U.S.C. §103(a).

7. Claims 11 and 25

Claims 11 and 25 specify the sample contains a detectable quantity of the antigen. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 11 and 25 are unpatentable under 35 U.S.C. §103(a).

8. Claims 12 and 26

Claims 12 and 26 specify that the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 12 and 26 are unpatentable under 35 U.S.C. §103(a).

9. Claims 13 and 27

Claims 13 and 27 specify that the insoluble carrier is a latex particle. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 13 and 27 are unpatentable under 35 U.S.C. §103(a).

10. Claims 14 and 28

Claims 14 and 28 specify that the insoluble carrier is silica or alumina. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 14 and 28 are unpatentable under 35 U.S.C. §103(a).

11. Claims 15 and 29

Claims 15 and 29 specify the insoluble carrier has an average particle size of 0.05 to 1 μm. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 15 and 29 are unpatentable under 35 U.S.C. §103(a).

12. Claims 16 and 30

Claims 16 and 30 specify that the sample is a buffered aqueous solution. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002.

Therefore, the Examiner has failed to meet the burden of proof that that Claims 16 and 30 are unpatentable under 35 U.S.C. §103(a).

13. Claims 18 and 32

Claims 18 and 32 specify the sample does not contain an immune reaction-accelerating component. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 18 and 32 are unpatentable under 35 U.S.C. §103(a).

14. Claims 19 and 33

Claims 19 and 33 specify that the immune reaction-accelerating component is polyethylene glycol 6000. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 19 and 33 are unpatentable under 35 U.S.C. §103(a).

15. Claims 20 and 34

Claims 20 and 34 specify that the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 20 and 34 are unpatentable under 35 U.S.C. §103(a).

16. Claims 35 and 39

Claims 35 and 39 specify that the antigen is apoprotein B. The Examiner has failed to provide any specific arguments why those claims are unpatentable over the cited references. See the Official Actions dated July 2, 2003 and July 16, 2002. Therefore, the Examiner has failed to meet the burden of proof that that Claims 35 and 39 are unpatentable under 35 U.S.C. §103(a).

X. RELIEF REQUESTED

Reversal of the Examiner's rejections of the appealed claims under 35 U.S.C. § 103(a) is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

James J. Kelly, PhD
Registration No. 41,504

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/03)

APPENDIX

The appealed claims, i.e., Claims 7-16, 18-30, 32-35, and 39 read as follows:

7. An agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is immobilized on an insoluble carrier, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is free,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

8. The immunoassay of Claim 7, wherein said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate.

9. The immunoassay according to Claim 7, wherein the amount of the antigen in the sample is determined from a calibration curve.

10. The immunoassay of Claim 7, wherein the sample contains an undetectable amount of the antigen.

11. The immunoassay of Claim 7, wherein the sample contains a detectable quantity of the antigen.

12. The immunoassay of Claim 7, wherein the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms.

13. The immunoassay according to Claim 7, wherein the insoluble carrier is a latex particle.

14. The immunoassay of Claim 7, wherein the insoluble carrier is silica or alumina.

15. The immunoassay of Claim 7, wherein the insoluble carrier has an average particle size of 0.05 to 1 μm.

16. The immunoassay of Claim 7, wherein the sample is a buffered aqueous solution.

18. The immunoassay of Claim 7, wherein the sample does not contain an immune reaction-accelerating component.

19. The immunoassay of Claim 18, wherein the immune reaction-accelerating component is polyethylene glycol 6000.

20. The immunoassay of Claim 18, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody.

21. An agglutination immunoassay for detecting an antigen in a sample, comprising:

(a) sequentially contacting the sample with

(i) a first antibody which is capable of specifically binding to a first binding site on the antigen, wherein the first antibody is free, and then

(ii) a second antibody which is capable of specifically binding to a second binding site on the antigen, wherein the second antibody is immobilized on an insoluble carrier,

thereby forming, when the antigen is present in the sample, an agglutinate comprising the first antibody, the antigen, and the second antibody; followed by

(b) optically measuring the amount of the agglutinate formed in (a); followed by

(c) correlating the amount of agglutinate formed with the amount of the antigen in the sample,

wherein the antigen is apoprotein B, HbA1C, serum amyloid A protein, or thrombin-antithrombin III complex.

22. The immunoassay of Claim 21, wherein said optically measuring comprises spectrophotometrically measuring decreasing light transmission due to formation of the agglutinate.

23. The immunoassay according to Claim 21, wherein the amount of the antigen in the sample is determined from a calibration curve.

24. The immunoassay of Claim 21, wherein the sample contains an undetectable amount of the antigen.

25. The immunoassay of Claim 21, wherein the sample contains a detectable quantity of the antigen.

26. The immunoassay of Claim 21, wherein the insoluble carrier is selected from the group consisting of organic polymeric substances, inorganic substances, cell membranes, hemocytes and microorganisms.

27. The immunoassay according to Claim 21, wherein the insoluble carrier is a latex particle.

28. The immunoassay of Claim 21, wherein the insoluble carrier is silica or alumina.

29. The immunoassay of Claim 21, wherein the insoluble carrier has an average particle size of 0.05 to 1 μm.

30. The immunoassay of Claim 21, wherein the sample is a buffered aqueous solution.

32. The immunoassay of Claim 21, wherein the sample does not contain an immune reaction-accelerating component.

33. The immunoassay of Claim 32, wherein the immune reaction-accelerating component is polyethylene glycol 6000.

34. The immnuoassay of Claim 21, wherein the first antibody is a monoclonal antibody and the second antibody is a polyclonal antibody.

35. The immunoassay of Claim 7, wherein the antigen is apoprotein B.

39. The immunoassay of Claim 21, wherein the antigen is apoprotein B.